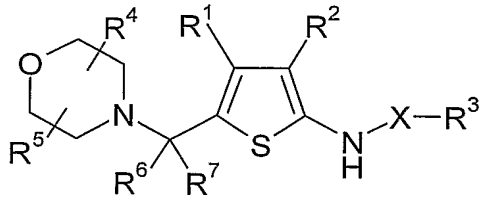
CLAIMS

1. A compound of the formula (I):



(I)

or a salt, solvate or N-oxide thereof, wherein:

R^1 and R^2 are the same or different and each is selected from hydrogen, saturated C_{1-3} hydrocarbyl, halogen and cyano;

X is selected from C=O, C=S, C(=O)NH, C(=S)NH, C(=O)O, C(=O)S, C(=S)O and C(=S)S;

R^3 is selected from aryl and heteroaryl groups each having from 5 to 12 ring members and being unsubstituted or substituted by one or more substituent groups R^{10};

R^{10} is selected from halogen, hydroxy, trifluoromethyl, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members; a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2, NR^c, SO_2NR^c or NR^cSO_2; and R^b is selected from hydrogen, carbocyclic and heterocyclic groups having from 3 to 12 ring members, and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di-C_{1-4} hydrocarbylamino, carbocyclic and heterocyclic groups having from 3 to 12 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2, NR^c, $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; or two adjacent groups R^{10}, together with the carbon atoms or heteroatoms to which they are attached may form a 5-membered heteroaryl ring or a 5- or 6-membered non-aromatic heterocyclic ring, wherein the said heteroaryl and heterocyclic groups contain up to 3 heteroatom ring members selected from N, O and S;

R^c is selected from hydrogen and C_{1-4} hydrocarbyl; and

X^1 is O, S or NR^c and X^2 is =O, =S or $=NR^c$;

R^4 and R^5 are the same or different and are selected from hydrogen and methyl; or one of R^4 and R^5 is selected from hydroxymethyl and ethyl and the other is hydrogen; and

R^6 and R^7 are the same or different and are selected from hydrogen and methyl.

2. A compound according to claim 1 wherein R^3 is a monocyclic aryl or heteroaryl group.

3. A compound according to claim 1 wherein R^3 is selected from unsubstituted or substituted phenyl, indenyl, tetrahydronaphthyl, naphthyl, pyridyl, pyrrolyl, furanyl, thienyl, imidazolyl, oxazolyl, oxadiazolyl, oxatriazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiadiazolyl (e.g. [1,3,4]-thiadiazolyl), pyrazolyl, pyrazinyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, tetrazolyl, benzfuranyl, chromanyl, thiochromanyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzthiazolyl and benzisothiazolyl, isobenzofuranyl, isoindolyl, indolizinyl, indolinyl, isoindolinyl, purinyl (e.g., adenine, guanine), indazolyl, benzodioxolyl, chromenyl, isochromenyl, chroman, isochromanyl, benzodioxanyl, quinolizinyl, benzoxazinyl, benzodiazinyl, pyridopyridinyl, pyrazolopyridine, pyrazolopyrimidine, pyrrolopyridine, pyrrolopyrimidine, quinoxalinyl, quinazolinyl, cinnolinyl, phthalazinyl, naphthyridinyl and pteridinyl.

4. A compound according to claim 2 wherein R^3 is a monocyclic aryl group.

5. A compound according to claim 2 wherein R^3 is a monocyclic heteroaryl group containing at least one nitrogen atom.

6. A compound according to claim 5 wherein the heteroaryl group is selected from pyrazolyl and thiadiazolyl (e.g. [1,3,4]-thiadiazolyl).

7. A compound according to any one of the preceding claims wherein the aryl group or heteroaryl group R^3 contains one or more substituent groups R^{10}

selected from halogen, carbocyclic and heterocyclic groups having from 4 to 7 ring members and optionally substituted C_{1-8} hydrocarbyl groups.

8. A compound according to claim 7 wherein the group R^3 contains a substituent R^{10} which is a carbocyclic or heterocyclic group having from 4 to 7 ring members.

9. A compound according to claim 8 wherein the carbocyclic or heterocyclic group is linked to the aryl or heteroaryl ring via a carbon nitrogen bond.

10. A compound according to claim 9 wherein the carbocyclic or heterocyclic group is a 4 to 7 membered (more typically 5 to 6 membered) heterocyclic group R^8 containing at least one nitrogen atom or oxygen atom ring member.

11. A compound according to claim 10 wherein R^8 is selected from morpholino, piperidino, piperazino, N-methyl piperazine, tetrahydrofuranyl and pyrrolidino.

12. A compound according to claim 11 wherein R^8 is morpholino.

13. A compound according to claim 11 wherein R^8 is tetrahydrofuranyl (e.g. 2-tetrahydrofuranyl).

14. A compound according to any one of the preceding claims wherein R^3 is a phenyl group bearing one or two *meta* substituents.

15. A compound according to claim 14 wherein one *meta* position on the phenyl ring is unsubstituted or is substituted by a group R^{10} selected from fluorine, chorine, methoxy, trifluoromethoxy, trifluoromethyl, ethyl, methyl and isopropyl; and the other *meta* position is substituted by a group selected from fluorine, chorine, methoxy, trifluoromethoxy, trifluoromethyl, ethyl, methyl, isopropyl, isobutyl, t-butyl, phenyl, substituted phenyl, and five and six membered monocyclic heterocyclic groups.

16. A compound according to claim 15 wherein both *meta* positions on the phenyl ring are substituted, one substituent being a halogen, preferably fluoro, and the other substituent being a group R^8 as defined in any one of claims 10 to 13.

17. A compound according to claim 16 wherein one substituent is fluorine and the other substituent is morpholine-4-yl.

18. A compound according to claim 8 wherein R^3 is a pyrazole group substituted by up to two substituent groups, for example 1 or 2 substituent groups.

19. A compound according to claim 18 wherein the pyrazole group is substituted by two substituent groups that are located on non-adjacent ring members.

20. A compound according to claim 18 or claim 19 wherein at least one of the substituents is located at a position *meta* or β with respect to the ring member linked to the group X.

21. A compound according to any one of claims 18 to 20 wherein the pyrazole group ring is substituted by an optionally substituted phenyl group (e.g. 4-fluorophenyl or 2,4-difluorophenyl) and a C_{1-4} hydrocarbyl group (e.g. *tert*-butyl).

22. A compound according to any one of the preceding claims wherein X is C=O or C(=O)NH.

23. A compound according to claim 22 wherein X is C=O.

24. A compound according to claim 22 wherein X is C(=O)NH.

25. A compound according to any one of the preceding claims wherein R^1 is selected from hydrogen, saturated C_{1-3} hydrocarbyl and halogen (e.g. chlorine and fluorine).

26. A compound according to any one of the preceding claims wherein R^2 is selected from hydrogen, saturated C_{1-3} hydrocarbyl and halogen (e.g. chlorine and fluorine).

27. A compound for use according to any one of the preceding claims wherein R^1 is a halogen.

28. A compound according to claim 27 wherein the halogen is chlorine.

29. A compound according to any one of the preceding claims wherein R^2 is a saturated C_{1-3} hydrocarbyl group.

30. A compound according to claim 29 wherein the saturated C_{1-3} hydrocarbyl group is methyl.

31. A compound according to any one of the preceding claims wherein the total number of carbon, halogen and nitrogen atoms making up the substituent groups R^1 and R^2 does not exceed 5.

32. A compound according to claim 31 wherein the total number of carbon, halogen and nitrogen atoms making up the substituent groups R^1 and R^2 is in the range 0 to 4, for example 0, 1, 2, or 3.

33. A compound according to any one of the preceding claims containing a combination of groups R^1 and R^2 selected from: (a) R^1 = chlorine & R^2 = methyl; (b) R^1 = chlorine & R^2 = hydrogen; (c) R^1 = hydrogen & R^2 = hydrogen; (d) R^1 = methyl & R^2 = hydrogen; (e) R^1 = cyano & R^2 = methyl; and (f) R^1 = methyl & R^2 = cyano.

34. A compound according to claim 3 wherein the combination of groups R^1 and R^2 is combination (a).

35. A compound according to any one of the preceding claims wherein R^4 is hydrogen.

36. A compound according to any one of the preceding claims wherein R^5 is hydrogen.

37. A compound according to any one of the preceding claims wherein R^6 is hydrogen.

38. A compound according to any one of the preceding claims wherein R^7 is hydrogen.

39. A compound according to any one of the preceding claims wherein when X is C=O or C=S and R^3 bears a substituent group R^a-R^b attached to an atom adjacent the atom in R^3 to which X is attached, and R^b is a carbocyclic or heterocyclic group or C_{1-8} hydrocarbyl substituted by a carbocyclic or heterocyclic group, then R^a is selected from a bond, O, CO, $X^1C(X^2)X^1$, S, SO and SO_2.

40. A compound according to any one of the preceding claims wherein, when X is CO, R^3 is other than a fused bicyclic aromatic or partially aromatic group bearing a substituent on a ring atom adjacent the ring atom to which X is attached.

41. A compound according to claim 1 which is selected from:

N-(4-chloro-3-methyl-5-(morpholin-yl methyl-thiophen-2-yl)-3-fluoro-morpholin-4-yl-benzamide;

1-[5-tert-butyl-2(4-fluoro-phenyl)-2H-pyrazol-3-yl]-3-(4-chloro-3-methyl-5-morpholin-4-ylmethyl-thiophen-2-yl) urea;

1-[5-tert-butyl-2-(2,4-difluoro-phenyl)-2H-pyrazol-3-yl]-3-(4-chloro-3-methyl-5-morpholin-4-ylmethyl-thiophen-2-yl)-urea; and

1-(4-chloro-3-methyl-5-morpholin-4-ylmethyl-thiophen-2-yl)-3-[5-(tetrahydro-furan-2-yl)-[1,3,4]thiadiazol-2-yl]-urea.

42. A compound according to any one of the preceding claims in the form of a salt, solvate or N-oxide.

43. A compound of the formula (I) as defined in any one of claims 1 to 42 for use in medicine, for example for use in therapy.

44. A pharmaceutical composition comprising a compound of the formula (I) as defined in any one of claims 1 to 42 together with a pharmaceutically acceptable carrier.

45. A pharmaceutical composition for administration by inhalation, the composition comprising a compound as defined in any one of claims 1 to 42 together with a pharmaceutically acceptable carrier.

46. A pharmaceutical composition according to claim 45 which is selected from inhalable dry powder compositions and aerosol compositions.

47. A compound of the formula (I) as defined in any one of claims 1 to 42 for use in the prophylaxis or treatment of a disease state or condition mediated by a p38 MAP kinase.

48. The use of a compound of the formula (I) as defined in any one of claims 1 to 42 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a p38 MAP kinase.

49. A method for the prophylaxis or treatment of a disease state or condition mediated by a p38 MAP kinase, which method comprises administering to a subject (e.g. a human subject) in need thereof a compound of the formula (I) as defined in any one of claims 1 to 42.

50. A method of inhibiting a p38 MAP kinase, which method comprises contacting the p38 MAP kinase with a kinase-inhibiting compound of the formula (I) as defined in any one of claims 1 to 42.

51. A method of modulating a cellular process by inhibiting the activity of a p38 MAP kinase using a compound of the formula (I) as defined in any one of claims 1 to 42, which method comprises bringing the compound of formula (I) into contact with a cellular environment containing the p38 MAP kinase.

52. A compound for use, use or method as defined in any one of claims 43 to 49 wherein the disease state or condition mediated by a p38 MAP kinase is selected from:

(i) inflammatory and arthritic diseases and conditions such as Reiter's syndrome, acute,synovitis, rheumatoid arthritis, osteoarthritis, rheumatoid spondylitis, gouty arthritis, traumatic arthritis, rubella arthritis, psoriatic arthritis, graft vs. host reaction and allograft rejections;

(ii) chronic inflammatory lung diseases such as emphysema, chronic pulmonary inflammatory disease, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome and acute respiratory distress syndrome (ARDS);

(iii) lung diseases and conditions such as tuberculosis, silicosis, pulmonary sarcoidosis, pulmonary fibrosis and bacterial pneumonia;

(iv) inflammatory diseases and conditions of the enteric tract such as inflammatory bowel disease, Crohn's disease and ulcerative colitis;

(v) toxic shock syndrome and related diseases and conditions such as sepsis, septic shock, endotoxic shock, gram negative sepsis and the inflammatory reaction induced by endotoxin;

(vi) Alzheimer's disease;

(vii) reperfusion injury;

(vii) diseases and conditions selected from atherosclerosis; muscle degeneration; gout; cerebral malaria; bone resorption diseases; fever and myalgias due to infection, such as influenza; cachexia, in particular cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS); AIDS; ARC (AIDS related complex); keloid formation; scar tissue formation; pyresis and asthma.

53. A compound for use, use or method as defined in claim 52 wherein the disease state or condition is selected from inflammatory diseases and conditions, rheumatoid arthritis and osteoarthritis.

54. A compound for use, use or method as defined in claim 52 wherein the disease state or condition is chronic obstructive pulmonary disease (COPD.

55. A compound of the formula (I) as defined in any one of claims 1 to 42 for use in the prophylaxis or treatment of a disease state or condition selected from the disease states and conditions set out in claims 52 to 54.

56. The use of a compound of the formula (I) as defined in any one of claims 1 to 42 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition selected from the disease states and conditions set out in claims 52 to 54.

57. A method for the prophylaxis or treatment of a disease state or condition selected from the disease states and conditions set out in claims 50 to 52, which method comprises administering to a subject (e.g. a human subject) in need thereof a compound of the formula (I) as defined in any one of claims 1 to 42.

58. A compound as defined in any one of claims 1 to 42 for use in the treatment or prophylaxis of a cancer.

59. The use of a compound as defined in any one claims 1 to 42 for the manufacture of a medicament for the treatment or prophylaxis of a cancer.

60. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a therapeutically effective amount of a compound as defined in any one of claims 1 to 42.

61. The use of a compound as defined in any one of claims 1 to 42 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition arising from abnormal cell growth.

62. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering

to the mammal a compound as defined in any one of claims 1 to 42 in an amount effective in inhibiting abnormal cell growth.

63. A method for alleviating or reducing the incidence of a disease or condition comprising or arising from abnormal cell growth in a mammal, which method comprises administering to the mammal a compound as defined in any one of claims 1 to 42 in an amount effective in inhibiting abnormal cell growth.

64. A method for alleviating or reducing the incidence of a disease state or condition disclosed herein, which method comprises administering to a patient (e.g. a patient in need thereof) a compound (e.g. a therapeutically effective amount) as defined in any one of claims 1 to 42.

65. A compound as defined in any one of claims 1 to 42 for use in the prophylaxis or treatment of a disease state or condition mediated by a raf kinase (such as B-raf or C-raf).

66. The use of a compound as defined in any one of claims 1 to 42 for the manufacture of a medicament for the prophylaxis or treatment of a disease state or condition mediated by a raf kinase (such as B-raf or C-raf).

67. A method for the prophylaxis or treatment of a disease state or condition mediated by a raf kinase (such as B-raf or C-raf)., which method comprises administering to a subject in need thereof a compound as defined in any one of claims 1 to 42.

68. A method for treating a disease or condition comprising or arising from abnormal cell growth in a mammal, the method comprising administering to the mammal a compound as defined in any one of claims 1 to 42 in an amount effective to inhibit raf kinase (such as B-raf or C-raf) activity.

69. A method of inhibiting a raf kinase (such as B-raf or C-raf), which method comprises contacting the kinase with a kinase-inhibiting compound as defined in any one of claims 1 to 42.

70. A method of modulating a cellular process (for example proliferation or cell division) by inhibiting the activity of a raf kinase (such as B-raf or C-raf) using a compound as defined in any one of claims 1 to 42.

71. A method for the diagnosis and treatment of a disease state or condition mediated by a raf kinase (such as B-raf or C-raf), which method comprises (i) screening a patient to determine whether a disease or condition from which the patient is or may be suffering is one which would be susceptible to treatment with a compound having activity against a raf kinase (such as B-raf or C-raf); and (ii) where it is indicated that the disease or condition from which the patient is thus susceptible, thereafter administering to the patient a compound as defined in any one of claims 1 to 42.

72. The use of a compound as defined in any one of claims 1 to 42 for the manufacture of a medicament for the treatment or prophylaxis of a disease state or condition in a patient who has been screened and has been determined as suffering from, or being at risk of suffering from, a disease or condition which would be susceptible to treatment with a compound having activity against a raf kinase (such as B-raf or C-raf).

73. A compound as defined in any one of claims 1 to 42 for use in the prophylaxis or treatment of inappropriate, excessive or undesirable angiogenesis.

74. The use of a compound as defined in any one of claims 1 to 42 for the manufacture of a medicament for the prophylaxis or treatment of inappropriate, excessive or undesirable angiogenesis.

75. A compound as defined in any one of claims 1 to 42 for use in the prophylaxis or treatment or alleviation of diseases or conditions, characterised by the up-regulation of a receptor tyrosine kinase, and in particular FGFR, Tie, VEGFR and/or Eph (more particularly a tyrosine kinase selected from FGFR-1, FGFR-2, FGFR-3, Tie2, VEGFR-2 and EphB2).

76. The use of a compound as defined in any one of claims 1 to 42 for the manufacture of a medicament for the prophylaxis or treatment or alleviation of diseases or conditions, characterised by the up-regulation of a receptor tyrosine kinase, and in particular FGFR, Tie, VEGFR and/or Eph (more particularly a tyrosine kinase selected from FGFR-1, FGFR-2, FGFR-3, Tie2, VEGFR-2 and EphB2).

77. A method of inhibiting angiogenesis *in vitro* or *in vivo*, comprising contacting a cell with an effective amount of a compound as defined in any one of claims 1 to 42.

78. A method for the treatment or alleviation of inappropriate, excessive or undesirable angiogenesis comprising administering to a subject suffering from said a disease or condition ameliorated by the inhibition of angiogenesis a therapeutically-effective amount of a compound as defined in any one of claims 1 to 42.

79. A method for the treatment of a disease or condition, preferably cancer, characterised by the up-regulation of a receptor tyrosine kinase comprising:

(i) diagnosing a subject suffering from a disease or condition, preferably cancer, characterised by the up-regulation or activating mutants of a receptor tyrosine kinase (for example a receptor tyrosine kinase selected from FGFR, Tie, VEGFR and Eph, and more particularly from FGFR-1, FGFR-2, FGFR-3, Tie2, VEGFR-2 and EphB2); and

(ii) administering to said subject a therapeutically-effective amount of a compound as defined in any one of claims 1 to 42.

80. A method for the treatment of diseases, for example cancers, with:

(a) activating mutants of ras or raf;

(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals; or

(d) upregulation of growth factor receptors, such as ERB2 and EGFR,

comprising:

(i) diagnosing a subject suffering from a disease with:

(a) activating mutants of ras or raf;

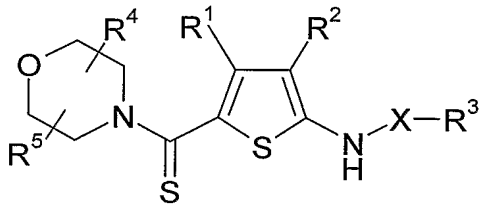
(b) upregulation of ras or raf;

(c) upregulated raf-MEK-ERK pathway signals; or

(d) upregulation of growth factor receptors, such as ERB2 and EGFR;

(ii) administering to said subject a therapeutically-effective amount of a raf kinase inhibitor compound as defined in any one of claims 1 to 42.

81. A process for the preparation of a compound as defined in any one of claims 1 to 42, which process comprises the S-alkylation (e.g. methylation) of a compound of the formula (X):



(X)

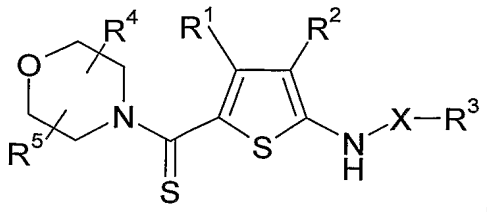
using an alkylating agent such as methyl iodide to give a thioimidate intermediate followed by:

(i) reduction of the thioimidate intermediate to give a compound of formula (I) in which R^6 and R^7 are hydrogen by means of a reducing agent such as a borohydride; or

(ii) treating the thioimidate intermediate with methyl lithium or a methyl Grignard reagent, followed by a reducing agent such as a borohydride to give a compound of the formula (I) in which one of R^6 and R^7 is methyl; or

(iii) treating the thioimidate intermediate with more than one equivalent of methyl lithium or a methyl Grignard reagent to give a compound of the formula (I) in which both R^6 and R^7 are methyl.

82. A compound of the formula (X):



(X)

wherein R^1 to R^5 and X are as defined in any one of claims 1 to 42.